# SYNTHETIC ORGANIC CHEMICALS

Quinoline and Its Derivatives

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QUINOLINE, C_9H_7N, was first observed in an impure form by Runge, in 1834, in coal distillates. In 1842 Gerhardt obtained the impure base by distillation of quinine with alkali, which lead to the name "quinoline." It also is found in bone oil. These sources constitute the principal natural ones. It is understood that quinoline obtained from coal tar has been available on the market. Commercial quantities are generally produced by synthetic methods, of which there are a number suitable for the preparation not only of quinoline itself but also of its many derivatives and homologues.

From the point of view of its synthesis, reactions, and isomerides, quinoline may, in general, be considered as naphthalene in which an alpha -CH- group has been replaced by nitrogen—
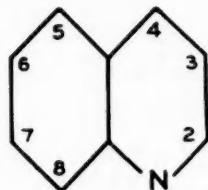

This similarity is pointedly demonstrated by the original method of synthesis employed by Königs (1879) in which quinoline is formed by ring closure of allylaniline, a procedure which is analogous to the formation of naphthalene from phenylbutylene.

The most familiar of the synthetic methods is Skraup's synthesis in which aniline, nitrobenzene, glycerin, and sulfuric acid are heated together. The nitrobenzene acts as an oxidizing agent and the reaction frequently proceeds with considerable violence. This can be abated, however, by the use of ferrous sulfate as an oxygen carrier, according to H. T. Clarke, or by replacing the nitrobenzene with arsenic acid, as suggested by Knüppel. Addition of boric or acetic acid has also been recommended. A great variety of substituted quinolines can be prepared by starting from substituted anilines and the corresponding nitro compound.

Another flexible method for the preparation of quinoline and its derivatives and homologues is that of Friedländer. The simplest illustration is the synthesis of quinoline from o-aminobenzaldehyde and acetaldehyde—
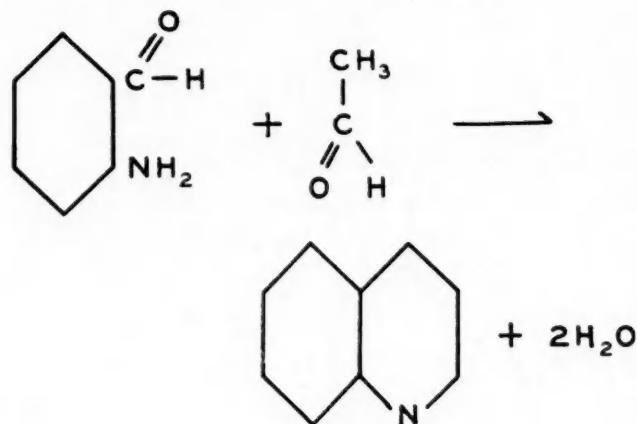
It is obvious that many variations of this procedure are possible since homologues and derivatives of o-aminobenzaldehyde can be used as the amine, while many aldehydes, ketones, ketoesters, etc., can be substituted for the acetaldehyde. The method can be extended to give not only purely organic substituents in the pyridine ring, but also groups such as nitro, as in the reaction of methazonic acid (from nitromethane and alkali) and o-aminobenzaldehyde to give 3-nitroquinoline—
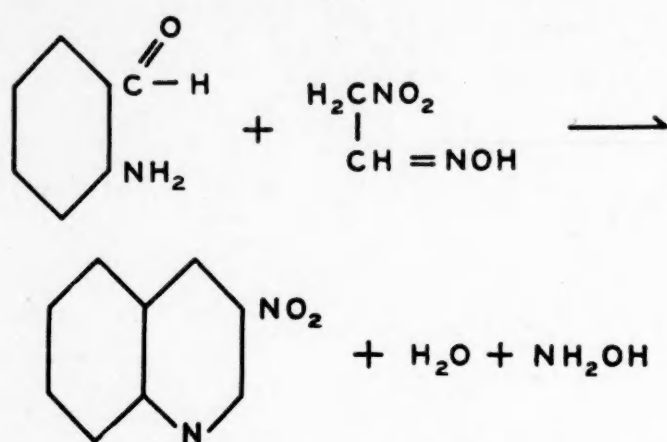
A fourth method of preparation is by the cyclization of o-amino compounds of benzene derivatives that have an oxygen atom attached to the third carbon atom of the side-chain, for example, o-aminocinnamaldehyde.

There are other methods of synthesis, but they are less versatile and will not be discussed here.

The quinolines are tertiary bases and in properties are very similar to pyridine. They form salts and double salts, and quinolinium compounds, the ease of formation being limited by the substituents present.

Quinoline is attacked by nitric or chromic acids only with difficulty. However, permanganate or hydrogen peroxide in the presence of iron or copper sulfate causes the production of quinolinic acid. Alkylquinolines in which the alkyl group is in either the benzene or pyridine nucleus are oxidized by chromic acid to the corresponding quinoline carboxylic acids, while permanganate oxidation of those substituted in the benzene ring re-

sults in carboxylic acids of pyridine. The 2-alkylquinolines, upon treatment with permanganate, yield acid derivatives of o-aminobenzoic acid. This is true also of quinolinium compounds.

As would be expected because of the lesser degree of aromaticity of the pyridine nucleus, substitution reactions with quinoline usually yield a product in which the substituent enters the benzene ring. An exception is bromination, which can be controlled to yield 3-bromoquinoline. Uncontrolled bromination yields a mixture of dibromoquinolines—nineteen having been identified.

Nitration of quinoline in the cold gives a mixture of 5-nitro- and 8-nitroquinolines, but if the reaction is carried out with heat, a mixture of the 5,7- and 6,8-dinitroquinolines is obtained.

Sulfonation proceeds in several ways, according to the conditions employed. If concentrated sulfuric acid at 220° C. is used, quinoline 8-sulfonic acid is obtained, whereas, if the temperature is raised above 300° C., the 6-sulfonic acid is formed. When oleum is used below 130° C., quinoline 7-sulfonic acid results; while at higher temperatures, the 5- and 8-sulfonic acids are formed.

Reduction, both by catalytic means and with nascent hydrogen, attacks the pyridine ring, causing the formation of tetrahydroquinoline. Under rigorous conditions, a hexahydroderivative is the final product.

Quinoline, like pyridine, does not acylate or alkylate in the Friedel-Crafts reaction. Apparently this failure is not due to complex formation with the ring nitrogen, since the acid chlorides and anhydrides of both the pyridine and the quinoline series readily acylate other aromatic structures.

Some of the quinoline derivatives are highly colored compounds and, therefore, have proved valuable as dyes. Included among the useful yellow dyes are quinophthalone, its sulfonic acid, and flavaniline (2-p-aminophenyl-4-methylquinoline). Quinophthalone is prepared

by the reaction of phthalic anhydride with 2-methylquinoline in the presence of zinc chloride; while flavaniline may be obtained by heating acetanilide with zinc chloride.

A great many derivatives of Alizarin Blue, particularly the sulfonic acids and polyhydroxy compounds, are important vat dyes. Alizarin Blue, which has the following formula,
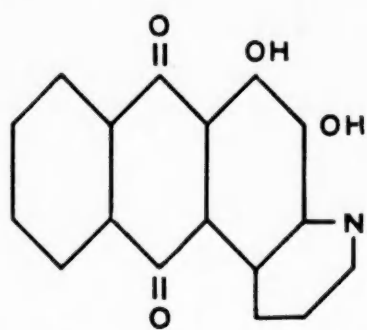

is prepared by the Skraup reaction, using β-aminoalizarin.

Quinoline derivatives are found in the series of cyanine dyes; an example (Quinoline Blue) is given below—
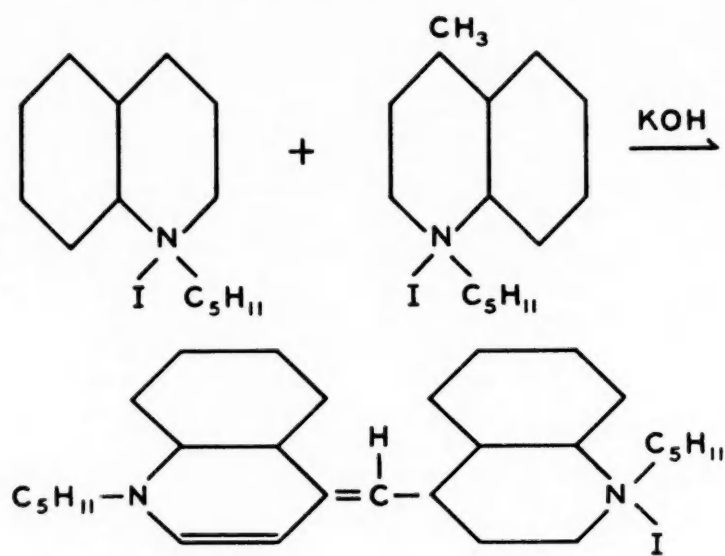
The compounds formed according to this scheme are blue dyestuffs. The isocyanines are joined through the 2 and 4' positions, instead of the 4 and 4' as in the cyanines, and are prepared by the action of alkali on quinolinehalogenalkylates and quinaldinehalogenalkylates. Pseudocyanines, joined through the 2 and 2' positions, are prepared by the reaction of 2-iodoquinolinehalogenalkylates with quinaldinehalogenalkylates. Both the isocyanines and pseudocyanines are red dyes.

One of the recent applications of quinoline derivatives is in inorganic analysis. They owe their usefulness as reagents to their ability to form co-ordination compounds according to the following schemes—
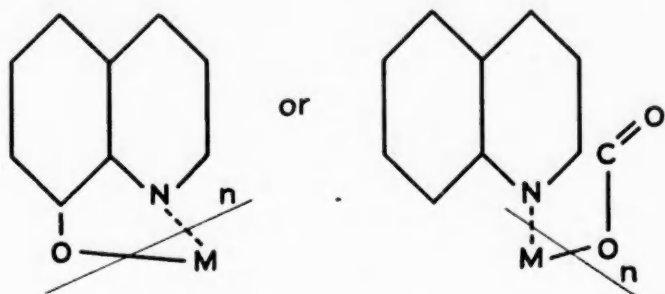
The most versatile of the compounds employed in this way is 8-hydroxyquinoline ("oxine"), which is used in the determination of bismuth, magnesium, zinc, aluminum, and cadmium—either gravimetrically, volumetrically by titration of the excess reagent with bromine, or colorimetrically by virtue of its reaction with phosphotungstomolybdic acid. Both 5,7-dichloro- and 5,7-dibromo-8-hydroxyquinolines are also used in this connection. Ferric iron can be determined colorimetrically with 7-iodo-8-hydroxyquinoline-5-sulfonic acid; by means of this reagent it is possible to detect as little as one part of ferric iron in ten million parts of solution. Quinoline-2-carboxylic acid is used in the gravimetric determination of copper, cadmium, and zinc.

Among the quinoline derivatives whose use in analysis is based upon complex formation with inorganic compounds are cinchonine, which gives a red precipitate with BiI_3; o-phenanthroline and 2-(2-pyridyl)quinoline, which exhibit great sensitivity toward ferrous salts; 6-nitroquinoline, which is used in the estimation of palladium; and β-naphthoquinoline which is used in gravimetric estimations of cadmium as the iodide.

From this brief summary of the principal properties and applications of quinoline and its many derivatives, it is readily apparent that this class of organic compounds is becoming very important in many fields of chemistry and industry.

Eastman Organic Chemicals as Analytical Reagents

XLIX REAGENTS FOR RARE EARTH METALS

METHYLENE BLUE

Reed, *Analyst*, **63**, 338 (1938)

Cerium can be determined by the formation of a blue color when methylene blue is added and the solution made alkaline. The aqueous test solution is made acidic with 5N sulfuric acid, then hydrogen peroxide and 0.5% methylene blue are added. After shaking, sodium hydroxide is added until the solution is distinctly basic. If as much as 1 p.p.m. of cerium is present, a blue color will result. Mercury, lead, bismuth, and molybdenum interfere, and must be removed before testing.

ARSANILIC ACID

Miller, *Ind. Eng. Chem., Anal. Ed.*, **9**, 181 (1937)

Ceric solutions form a red-brown color upon the addition of arsanilic acid. The test is very sensitive and can be used for the qualitative detection of cerium in the presence of elements with which it is commonly found. The reagent can be used as an outside indicator in ceric sulfate titrations.

4,4'-TETRAMETHYLDIAMINOTRIPHENYL-METHANE

Ku'lberg, *Mikrochemie*, **21**, 35 (1936)

Cerium reacts in acid solution to change the color of 4,4'-tetramethyldiaminotriphenylmethane to blue-green.

The cerium is precipitated as $Ce(OH)_3$ which autooxidizes in air to $Ce(OH)_4$. A drop of the reagent in sulfuric acid is added, and the presence of cerium is shown by the appearance of a blue-green to green coloration. As little as 0.03γ of metal can be detected.

BRUCINE

Shemyakin, Volkova, and Bozhko, *J. Gen. Chem. (U.S.S.R.)*, **8**, 452 (1938)

Cerium is the only element which gives a color reaction with brucine. The test solution is slightly acidified with sulfuric acid, and a solution of brucine acetate added. The amount of cerium present can be determined by comparing with color standards the orange-red color that is formed.

CACOTHELINE

Beck, *Mikrochim. Acta*, **3**, 141 (1938)

Bivalent europium reduces cacotheline to a violet dye. The reaction is similar to that of titanium, tin, vanadium, columbium, molybdenum, tungsten, uranium, and rhenium in the lower states of oxidation. Since other rare earths do not give a similar test, it is possible to detect europium in mixtures of them. Reduction of the metal is accomplished by means of zinc in the presence of acid.

8-HYDROXYQUINOLINE

Pirtea, *Z. anal. Chem.*, **107**, 191 (1936)

Lanthanum can be determined quantitatively through the precipitate formed with 8-hydroxyquinoline. The reagent is added to an acetic acid solution of lanthanum nitrate, and ammonia added until the solution is strongly ammoniacal. The precipitate of lanthanum hydroxyquinolate may be dried and weighed as such, or analyzed volumetrically.

New Eastman Chemicals

2759	Benzotriazole
4633	1,5-Dihydroxynaphthalene Diacetate
4658	s-Dimethyloxamide
4309	2,4-Dinitrobenzenesulfonic Acid
3934	Ethyl Nicotinate
P4662	Ethyl Phosphate (Pract.)
4383	Methyl Cholanthrene
P4656	β-Naphthoyl Chloride (Pract.)
P4653	1-Nitro-2-methylanthraquinone (Pract.)
P4652	Phorone (Pract.)
4661	Sorbitol Hexaacetate